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(54) Title: STAPHYLOCOCCUS EPIDERMIDIS NUCLEIC ACIDS AND PROTEINS

(57) Abstract: S epidermidis polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques is disclosed. Also disclosed are methods for utilizing such polypeptides and DNA (RNA) for the treatment of infection, particularly infections arising from S epidermidis. Antagonists against the function of such polypeptides and their use as therapeutics to treat infection are also disclosed. Also disclosed are diagnostic assays for detecting diseases related to the presence of S epidermidis nucleic acid sequences and the polypeptides in a host. Also disclosed are diagnostic assays for detecting polynucleotides and polypeptides related to S epidermidis.

STAPHYLOCOCCUS EPIDERMIDIS NUCLEIC ACIDS AND PROTEINS

Field of the Invention

The present invention provides nucleic acids, and peptides, polypeptides and proteins encoded by the nucleic acids, isolated from *Staphylococcus*
5 *epidermidis*.

Background of the Invention

Staphylococcus epidermidis is a gram-positive bacteria present in the normal flora of humans, and is typically present on the skin. It is catalase positive
10 and grows aerobically. It is implicated in various human conditions and diseases, including subacute bacterial endocarditis (Baddour LM et al., Production of experimental endocarditis by coagulase-negative staphylococci: variability in species virulence, J. Infect. Dis. 150: 721-727, 1984; Karchmer AW, Archer GL, Dismukes WE, *Staphylococcus epidermidis* causing prosthetic valve endocarditis:
15 microbiologic and clinical observations as guides to therapy, Ann Intern Med. 1983;98:447-455.) and septicemia (Christensen GD et al., Nosocomial septicemia due to multiply antibiotic-resistant *Staphylococcus epidermidis*, Ann. Intern. Med. 96: 1-10, 1982). *S. epidermidis* is estimated to be responsible for about 12% of all hospital patient infections. Because of the organism's peculiar ability to colonize
20 polymer and metallic surfaces, there is a correlation of infection with the insertion of intravenous lines or catheters or implantation of prosthetic devices. Treatment can be difficult since different isolates of *S. epidermidis* show a broad spectrum of antibiotic resistance. The organism also produces a polysaccharide biofilm which helps to protect the bacteria from the human immune system (Tojo M et al.,
25 Isolation and characterization of a capsular polysaccharide adhesin from *Staphylococcus epidermidis*, J. Infect. Dis. 157: 713-722, 1988).

The present invention advantageously provides isolated nucleic acids and their encoded peptides, polypeptides and proteins from the genome of *S. epidermidis*, as well as the genomic map of *S. epidermidis*. Thus, the present
30 invention fulfils a a widely-felt need for *S. epidermidis* diagnostics, antigens, and

About 26 different isolates of *S. epidermidis* have been submitted to ATCC listed in their on-line catalog, listed below:

- 1: ATCC Number: 146 Organism: *Staphylococcus epidermidis*
- 2: ATCC Number: 33501 Organism: *Staphylococcus epidermidis*
- 5 3: ATCC Number: 49741 Organism: *Staphylococcus epidermidis*
- 4: ATCC Number: 51625 Organism: *Staphylococcus epidermidis*
- 5: ATCC Number: 29997 Organism: *Staphylococcus epidermidis*
- 6: ATCC Number: 19654 Organism: *Staphylococcus epidermidis*
- 7: ATCC Number: 14389 Organism: *Staphylococcus sp. deposit*
- 10 8: ATCC Number: 14852 Organism: *Staphylococcus epidermidis*
- 9: ATCC Number: 49134 Organism: *Staphylococcus epidermidis*
- 10: ATCC Number: 13518 Organism: *Staphylococcus epidermidis*
- 11: ATCC Number: 9491 Organism: *Staphylococcus epidermidis*
- 12: ATCC Number: 35547 Organism: *Staphylococcus epidermidis*
- 15 13: ATCC Number: 35984 Organism: *Staphylococcus epidermidis*
- 14: ATCC Number: 35983 Organism: *Staphylococcus epidermidis*
- 15: ATCC Number: 700296 Organism: *Staphylococcus epidermidis*
- 16: ATCC Number: 49461 Organism: *Staphylococcus epidermidis*
- 17: ATCC Number: 29641 Organism: *Staphylococcus epidermidis*
- 20 18: ATCC Number: 29887 Organism: *Staphylococcus epidermidis*
- 19: ATCC Number: 29886 Organism: *Staphylococcus epidermidis*
- 20: ATCC Number: 55133 Organism: *Staphylococcus epidermidis*
- 21: ATCC Number: 27626 Organism: *Staphylococcus sp. deposit*
- 22: ATCC Number: 31874 Organism: *Staphylococcus epidermid*
- 25 23: ATCC Number: 14990 Organism: *Staphylococcus epidermid*
- 24: ATCC Number: 155 Organism: *Staphylococcus sp. deposit*
- 25: ATCC Number: 155-U Organism: *Staphylococcus sp. depos*
- 26: ATCC Number: 12228 Organism: *Staphylococcus epidermid*

30 Throughout this application, various publications are referenced. These publications are hereby incorporated by reference in their entirety.

While the invention has been described with respect to certain specific embodiments, it will be appreciated that many modifications and changes may be made by those skilled in the art without departing from the spirit of the invention.

35 It is intended, therefore, by the appended claims, to cover all such modification and changes as fall within the true spirit and scope of the invention.

What is claimed is:

1. An isolated polynucleotide comprising a member selected from the group consisting of:
 - (a) a polynucleotide encoding a polypeptide having at least a 70% identity to a polypeptide set forth in the Sequence Listing;
 - (b) a polynucleotide which is complementary to the polynucleotide of (a);and
 - (c) a polynucleotide comprising at least 15 sequential bases of the polynucleotide of (a) or (b).
2. The polynucleotide of Claim 1 wherein the polypeptide has at least 80% identity to the polypeptide set forth in the Sequence Listing.
3. The polypeptide of Claim 2 wherein the polypeptide has at least 90% identity to the polypeptide set forth in the Sequence Listing.
4. The polynucleotide of Claim 1 wherein the polynucleotide is DNA.
5. The polynucleotide of Claim 1 wherein the polynucleotide is RNA.
6. The polynucleotide of Claim 4 wherein the polynucleotide has at least 80% identity to a polynucleotide set forth in the Sequence Listing.
7. The polynucleotide of Claim 6 wherein the polynucleotide has at least 90% identity to a polynucleotide set forth in the Sequence Listing.
8. The polynucleotide of Claim 4 comprising a polynucleotide set forth in the Sequence Listing.
9. The polynucleotide of Claim 4 comprising a polynucleotide set forth in the Sequence Listing as any of an odd-numbered SEQ ID Nos 1-3334.
10. An isolated polynucleotide comprising a member selected from the group consisting of:
 - (a) a polynucleotide having at least a 70% identity to a polynucleotide contained in any of ATCC Deposit Nos. 146; 33501; 49741; 51625; 29997; 19654 ; 14389 ; 14852 ; 9134 ; 13518; 9491; 35547 ; 35984; 35983; 700296; 49461; 29641; 29887 ; 29886; 55133; 27626; 31874; 14990; 155; 155-U; 12228 and substantially encoding the polypeptide comprising amino acids 1 to 416 of SEQ ID NO:2;
 - (b) a polynucleotide complementary to the polynucleotide of (a); and
 - (c) a polynucleotide comprising at least 15 sequential bases of the polynucleotide of (a) or (b).

11. A vector comprising the DNA of Claim 4.
12. A host cell comprising the vector of Claim 11.
13. A process for producing a *S. epidermidis* polypeptide comprising expressing from the host cell of Claim 12 a polypeptide encoded by said DNA.
14. A process for producing a cell which expresses a *S. epidermidis* polypeptide comprising transforming or transfecting the cell with the vector of Claim 11 such that the cell expresses the polypeptide encoded by the DNA contained in the vector.
15. A polypeptide comprising an amino acid sequence which is at least 70% identical to a polypeptide set forth in the Sequence Listing.
16. A polypeptide comprising an amino acid sequence which is at least 80% identical to a polypeptide set forth in the Sequence Listing.
17. A polypeptide comprising an amino acid sequence which is at least 90% identical to a polypeptide set forth in the Sequence Listing.
18. A polypeptide comprising an amino acid sequence as set forth in the Sequence Listing.
19. An antibody against the polypeptide of claim 18.
20. An antagonist which reduces or inhibits the activity of the polypeptide of claim 18.
21. A method for the treatment of an individual having need to reduce or inhibit the activity of the polypeptide of Claim 18 comprising administering to the individual a therapeutically effective amount of the antagonist of Claim 20.
22. A complex of a polypeptide and a binding molecule which comprises the polypeptide of Claim 18 and a binding molecule that is capable of antagonising the activity of the polypeptide.
23. A process for diagnosing in a subject a disease related to expression of the polypeptide of claim 18 comprising detecting the presence in the subject of a nucleic acid sequence encoding said polypeptide.
24. A diagnostic process comprising detecting the presence of the polypeptide of claim 18 in a sample derived from a subject.
25. A method for identifying compounds capable of inhibiting the activity of the polypeptide of claim 18 comprising:
 - (a) contacting a cell expressing the polypeptide on the surface thereof with a selected compound, under conditions to permit binding to the polypeptide in the presence of a component capable of providing a detectable signal in response to the binding of the compound to said polypeptide; and

(b) detecting the presence or absence of a signal generated in response to the binding of the compound to the polypeptide,
the presence of a signal indicating a compound capable of inhibiting the activity of the polypeptide.

26. A method for inducing an immunological response in a mammal which comprises inoculating the mammal with the polypeptide of Claim 15, or a fragment or variant thereof, adequate to protect said animal against infection from *S. epidermidis*.

27. A method of inducing an immunological response in a mammal which comprises delivering a gene encoding the polypeptide of Claim 15, or a fragment or variant thereof, and obtaining expression of the gene *in vivo* in order to induce an immunological response to produce antibody to protect said animal against infection from *S. epidermidis*.

28. An immunological composition comprising a DNA capable of expressing a polypeptide of Claim 15 which, when introduced into a mammal, induces an immunological response in the mammal, and a pharmaceutically acceptable carrier.

29. An immunological composition comprising a polypeptide of claim 15 which, when introduced into a mammal, induces an immunological response in the mammal, and a pharmaceutically acceptable carrier.

rfa, MnhA, MnhB, MnhC, MnhD, MnhE, MnhF and MnhG, complete c
ds. NID: g4001723.

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Sequence 2026

25 MFMLIGIIGSFTTGDIFNLFVFFEVFLMSSYCLLVIGTTKIQLQETIKYILVNVVSSSFF
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AYYAPPVAIITFFGALLTKVGVIARTLSLFFNNTVSFSHYVILFLALLTIIFGCIGAI
AYYDTKKIILYNIMIAVGVILVGIAMNESGMTGAIYYTLHDMLVKASLFLIGVYKIT
KTDLRHFGGLIKGYPILGWTFIFIAALSLAGIPPFSGFYGKFYIVRATFEKGFYLSGIIIV
30 LLSSLIVLYSVIRIFLKGFFGEVEGYTSLSKVNVKYLTTIAVASTVITVIFGLSADTLFP
IIKDGAETFVDPSQYIHSVLGGK*

Sequence 2027

35 Contig_0696_pos_1081_776,
is similar to (with p-value 3.0e-40)
>gp:gp|AB015981|AB015981_6 Staphylococcus aureus genes for O
rfa, MnhA, MnhB, MnhC, MnhD, MnhE, MnhF and MnhG, complete c
ds. NID: g4001723.
atgcttatcattacatttttaactgagttataaaaagcaaaactttggtgtactaaaaatt
40 attctcaaaccacgaattgagaataaaacccggattctttgtgtacgagacggaattagaa
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gaagaagagattcaaaatatcaaatcttcattagagaaggtcggttagaaaggtaggcgag
aaataa
45

Sequence 2028

MLIITFLTELIKANFGVLKIIILKPRIENKPGFFVYETELERDWQLVLLSNLITLTPGTVV
LGISDDRKKIYIHSIDFSTKEEEIQNIKSSLEKVVVRKVGK*

Sequence 2029

50 Contig_0697_pos_2646_3434,
is similar to (with p-value 3.0e-34)
>sp:sp|P06696|TNPA_STAAU TRANSPOSASE A (TRANSPOSON TN554). >
pir:pir|A24584|A24584 transposition regulatory protein tnpA
55 - Staphylococcus aureus transposon Tn554 >gp:gp|X03216|ISTN5
54_1 Staphylococcus aureus transposon Tn554. NID: g43726. >g
p:gp|K02987|TRN554_1 Transposon Tn554 (from S.aureus), compl
ete, containing transposition genes tnpA, tnpB and tnpC, and
antibiotic resistance genes ermA and spc. NID: g154920.

gtgtatacttatactattataaaattagaaatgagattattatgaaaatagtagaagtaaaa
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cccgaactaa

15 Sequence 2030
VYTYTIKIRNEIIMKIVEVKSNGTNFMILDGNNEPIVDAVRYLKYLDVSKKSLNKKTY
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MTVVSNFYDYLRSKKLDVNFYDFMHMESKYSKKYKSFMHINKDYRTLKNILKVKEPKK
20 KIEVLTAIEVKKLLLEANNIRDKFLIQLLYETGLRIGEVLSLRIDDIKFDFRNPSIKTIL
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Sequence 2031
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25 putative peptide of unknown function
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30 cgtcacaccacgagagtttgtaacacccgaagccgggtggagtaaccatttggagctagcc
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Sequence 2032
VTNRRKVGMTSNHHAPYDLGYTRATMDNTKGSETARSSKSHKVLSSDCSLQLDYMKLES
35 LVIVDQHATVNTFPGLVHTARHTTRVCNTRSRSWSNHLELAVEGGTNDWGEVVTR*

Sequence 2033
Contig_0697_pos_1439_399,
putative peptide of unknown function
40 atgcaaaaagtacgtttctgatataatgactcatcggtgttctcactatgatttaggagta
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Sequence 2034

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25

Sequence 3821

step.1023e01.cons.ok

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CATGGATTAAATTAATGATTATAATTCTTAGTAGAGGAGTGAGGCTTCC
GTGGAAGAACGATTAAATCGCGTGAAGCAACAATTACAACAATCTTCATAT
AAATTGACTCCACAAAGAGAGGCAACTGTTAGAGTATTAATTGAAAATGAA
AAAGATCATCTTAGCGCAGAAGATGTGTACTTAAAAGTCAAAGATAAGGCT
25 CCAGAAAATAGGATTAGCTACCGTTTATAGAATTTAGAAATGCTAGCTGAA
ATAAAAGTGCTAGATAAAATAAATTTTGGTGATGGTGTAGCTCGTTTTGAT
TTAAGAAAAGAAGGAGCCAAGCATTTCATCATCA

30 Sequence 3822

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TGTACCACTTACTCCAAAAATATCTCCAAGAACGACATAACCTACGTAACC
GATTGTTGATAGAAGTAATATTTCCCATTTGCTTTTTTTAAATTTCTGGGTATC
GGATTTGCCTTCGCTTTTGGCTTTAAGTGATGTTAAAGAAATACCTACAAC
35 CAATAAGATCATTGCTATAAGTCCCATCACTACTTGAACAATCGTGCTCCA
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40 TCCGATAAAAAGTGACCTAAAGTTGTACCTCGAATCTGATTATATGGTCC
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AGAACAAAATTAAGTGTCCTCAATTACACTCGAAATCATTCTATAGTAATTA
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50 ATATAGAAGGGAAACAGTATATAGTAACCTGGGCATTGGGGCATCTTGTGA
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ATGCACAATTATCATTAGGTCGTGTACAACTCCAACAATACAAATAGTTA

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DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: STAPHYLOCOCCUS EPIDERMIDIS NUCLEIC ACIDS AND PROTEINS

(57) Abstract: S epidermidis polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques is disclosed. Also disclosed are methods for utilizing such polypeptides and DNA (RNA) for the treatment of infection, particularly infections arising from S epidermidis. Antagonists against the function of such polypeptides and their use as therapeutics to treat infection are also disclosed. Also disclosed are diagnostic assays for detecting diseases related to the presence of S epidermidis nucleic acid sequences and the polypeptides in a host. Also disclosed are diagnostic assays for detecting polynucleotides and polypeptides related to S epidermidis.

WO 01/34809 A3

INTERNATIONAL SEARCH REPORT

International Application No

PL./US 00/30782

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/31 C07K14/31 C07K16/12 C12Q1/68 G01N33/53
 A61K39/085 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N C12Q G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, EMBL, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL [Online] EBI; ACC.NO: M33228, 5 February 1991 (1991-02-05) BHAT ET AL.: "T.brucei kinetoplast ATPase 6 edited mRNA, complete cds." XP002163041 abstract</p> <p style="text-align: center;">--- -/--</p>	1

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "8" document member of the same patent family

Date of the actual completion of the international search

16 March 2001

Date of mailing of the international search report

20. 06. 01

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van Klompenburg, W

INTERNATIONAL SEARCH REPORT

International Application No

PL./US 00/30782

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VAN DE KAMP ET AL.: "Elucidation of the primary structure of the lantibiotic epilancin K7 from Staphylococcus epidermidis K7. Cloning and characterisation of the epilancin-K7-encoding gene and NMR analysis of mature epilancin K7" EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 230, no. 2, 1 June 1995 (1995-06-01), pages 587-600, XP000990390 figures 3,4 ---	1-29
A	US 5 587 307 A (ALBORN JR WILLIAM E ET AL) 24 December 1996 (1996-12-24) column 2, line 28 - line 34; claims 1-5 ---	1-29
A	US 5 770 375 A (EDA SOJI ET AL) 23 June 1998 (1998-06-23) figure 2; tables 1-3 ---	1-29
A	US 5 961 975 A (KARAKAWA WALTER W ET AL) 5 October 1999 (1999-10-05) claims 1-12; examples 3-9 -----	19-29

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

page 2 of 2

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 00/30782

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 21,26,27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-9, 11-29, all partially, 10 compl.

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1; claims 1-9,11-29, all partially,
10 completely

An isolated polynucleotide comprising a member selected from the group consisting of: a) a polynucleotide encoding a polypeptide with at least a 70% identity to SEQ ID NO:2 b) A complementary polynucleotide. c) a polynucleotide comprising at least 15 sequential bases of the polynucleotide of (a) or (b).

A vector comprising said polynucleotide and a host cell comprising said vector. A process for producing a S. epidermidis polypeptide encoded by the above mentioned polynucleotide and a process for producing a cell which expresses said polypeptide. A polypeptide comprising an amino acid sequence which is at least 70% identical to SEQ ID NO:2. An antibody against a polypeptide comprising the amino acid sequence of SEQ ID NO:2. An antagonist which reduces or inhibits the activity of said polypeptide. A complex of said polypeptide and a binding molecule. A method of treatment, a method of diagnosis. A method to identify compounds capable of inhibiting the activity of said polypeptide. A method for inducing an immunological response. An immunological composition.

2. Claims: Inventions 2-1667; claims 1-9,11-29, all partially

As for invention 1, but each invention is limited to each one of the individual polypeptides with the sequences of the even numbers of SEQ ID NO: 4-3334 encoded by the polynucleotides with the sequences of the odd-numbers of SEQ ID NO:3-3334.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 20-22 relate to a compound defined by reference to a desirable characteristic or property, namely antagonising, inhibiting or reducing the activity of the polypeptide of the invention

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the antibodies and antisense molecules with antagonist activity mentioned in the description at pages 32

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PL./US 00/30782

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5587307 A	24-12-1996	AU 6180294 A CA 2122202 A EP 0625575 A HU 70300 A JP 6319561 A	03-11-1994 31-10-1994 23-11-1994 28-09-1995 22-11-1994
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